REMARKS/ARGUMENTS

Claims 1-28 are currently pending in the above-identified application. Claims 14-28 were previously withdrawn by the Examiner as being drawn to a non-elected invention. With this amendment, claim 1 is amended. Support for these amendments is identified in the following remarks. No new matter is added by these amendments. Examination and reconsideration of all pending claims are respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement is submitted herewith together with a copy of the reference numbered "AO" in the Information Disclosure Statement filed on August 29, 2001. While the English translation/Abstract of the reference itself is not available, the Supplemental IDS submitted herewith specifically cites to portions of the reference that are either in English or show peptide synthesis schematics that use internationally recognized symbols and abbreviations. The relevant information is on pages 86 (Diagram 5), 88 (Diagram 7), and 95 (English Summary).

Applicants therefore submit that the Supplemental IDS filed herewith complies with the provisions of 37 CFR § 1.97, 1.98 and MPEP § 609.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-13 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that term "substantial portion" in claim 1 is a relative term rendering the claim indefinite. The Examiner also asserts that the claims are indefinite for reciting "a substantial portion of the composition comprising the immobilized peptide comprises peptide" and for reciting "an intramolecular disulfide bond" between the two Cys residues.

The present rejection is obviated by the deletion from claim 1 of the phrase "wherein a substantial portion of the composition comprising the immobilized peptide comprises peptide having an intramolecular disulfide bond between the two Cys residues." Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1, 2, 4 and 6-9 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Cosand *et al.* (U.S. Patent No. 4,269,783). This rejection is traversed in part and overcome in part for the reasons set forth below.

Claim 1 is amended to recite that the "thiol groups of the Cys residues are reversibly protected from oxidation by a chemically reversible means resistant to highly acidic cleavage conditions." Support for this amendment is found in the specification as filed at, *e.g.*, page 4, lines 22-27.

The Examiner, citing to column 9, lines 54-64 of Cosand, contends that in Cosand "the thiol groups of the Cys residues are reversibly protected from oxidation by a chemically reversibl[e] mean[s]." (*See* Office Action at page 5, lines 9-11.) The cited passage of Cosand states the following:

> Peptide I was assembled on a t-butyloxy-carbonyl (BOCD)-methylbenzylcysteine-phenyl-acetamidomethyl (PA) polystyrene/divinlybenzene resin .... Symmetrical anhydride couplings were carried out in an Applied Biosystems 430A synthesizer. ***Benzyl based*** side chain protection and BOC alpha-amine protection were used. Tryptophan was protected by the formyl moiety and methionine by it sulfoxide, both protecting groups being removed by conventional procedures. [Emphasis added.]

It was well-known in the art of peptide synthesis that benzyl-based side chain protection is conventionally removed at the same time as cleavage of the peptide from the supporting resin by exposure of the resin-bound peptide to highly acidic conditions (*e.g.*,

exposure to hydrofluoric acid (HF) and/or trifluoroacetic acid (TFA)). In this regard, Applicants also note that the application itself specifically distinguishes "chemically reversible protection means resistant to highly acid cleavage conditions" from benzyl based blocking:

> Peptides are synthesized using standard solid phase peptide synthesis methods ***with the exception that a chemically reversible protection means resistant to the highly acidic cleavage conditions is substituted for commonly used S-benzyl blocking*** of cysteine thiol groups. [Page 4, lines 22-27 (emphasis added).]

Accordingly, for at least for the reasons stated above, amended claim 1 and all claims depending therefrom are novel over Cosand.

While Applicants believe claim 1 and all dependent claims to be novel over Cosand as set forth above, Applicants wish to specifically address the present rejection as it pertains to dependent claim 2, which recites, *inter alia*, protection of the Cys residues from oxidation by acetamidomethyl. The Examiner states the following:

> [a]lthough Cosand et al. is silent on the protection of Cys residues present in peptide of formula (I) with acetamidomethyl[,] free phenyl-acetamidomethyl ions, including acetomidomethyl would necessarily react with the Cys residues to yield a Cys-acetamidomethyl conjugate. The resulting conjugate would necessarily be protected from oxidation.
>
> [Office Action dated 3/23/2005 at page 6 (emphasis provided).]

Thus, the Examiner appears to rely on inherency in setting forth the present rejection of claim 2. Applicants respectfully note that to support an anticipation rejection based on an alleged inherent disclosure of a claim limitation, the Examiner must show that the limitation at issue would necessarily flow from the teachings of the applied reference. (MPEP § 2112 (IV).) Here, the Examiner has not shown where Cosand describes a set of circumstances in

which unprotected Cys residues of a peptide synthesized on a BOCD resin would encounter free acetamidomethyl. The Examiner has not shown where Cosand itself describes the use of free acetamidomethyl. Further, even assuming (for arguments sake only) the presence of free acetamidomethyl, Applicants note that the peptides of Cosand are synthesized on a BOCD resin using amino acids already having benzyl side chain protection; thus, there would not be any unprotected Cys residues available to form a Cys-acetamidomethyl conjugate.

For the reasons above, Applicants believe claims 1, 2, 4 and 6-9 to be novel over Cosand *et al.* under 35 U.S.C. § 102(b). Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Cosand in view of Brugger

Claim 3 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cosand *et al.* (U.S. 4,629,783) in view of Brugger *et al.* (U.S. 3,798,203). This rejection is traversed in part and overcome in part for the reasons set forth below.

Claim 1 is amended to recite that the isolated peptide is "immobilized on a solid phase suitable for use in an immunological assay." Support for this amendment is found in the specification at, *e.g.*, page 4, lines 15-19. Applicants note that this amendment distinguishes the recited "solid phase" from a solid phase used during synthesis of a peptide (*e.g.*, from the "t-butyloxy-carbonyl (BOCD)-methylbenzylcysteine-phenyl-acetamidomethyl (PA) polystyrene/divinlybenzene resin" disclosed in Cosand, or other resin supports used for peptide synthesis). Accordingly, Applicants also note that claim 1 as amended recites a peptide antigen in a form following (a) synthesis of the peptide, (b) cleavage of the peptide from a solid support used in such synthesis, and (c) immobilization of the peptide onto a solid phase.

Applicants also note that the composition as recited in the present claims provides certain technical advantages over previous peptide antigen compositions. In particular, because

the peptide antigen is both (1) immobilized on a solid phase suitable for use in immunassays and (2) comprises Cys residues "reversibly protected from oxidation by a chemically reversible means," the oxidative form of the peptide antigen can be controlled while the peptide is in an immobilized state amenable to immunological diagnostic applications. As noted in the present application, previous peptide compositions comprise a mixture of a variety of oxidative forms, and precautions are generally not taken to control the oxidative form of peptides immobilized on a solid phase. (Specification at page 3, lines 23-28.) Such a variety of oxidative forms of the peptides can be a source of variability in sensitive immunoassays, which can influence the results based on those assays. (*Id.* at page 4, lines 1-4.) For example, in some cases, the cyclic form of certain peptides is less efficient at binding to solid surfaces than polymeric forms. (*Id.* at page 3, line 36, to page 4, line 1.) Further, formation of intramolecular disulfide bonds can contribute to the conformation of the peptide capable of binding antibodies engendered by the native protein. (*See id.* at page 8, line 27-31.) Thus, hindering the development of such oxidative forms during synthesis while providing for control of the oxidative form after synthesis and immobilization provides for improved reactivity in immunological assays (*e.g.*, increased sensitivity and/or specificity). (*See, e.g., id.* at page 8, lines 18-23.)

The cited references, alone or in combination, do not teach or suggest the composition as presently recited in amended claim 1. Neither Cosand nor Brugger teach or suggest immobilization, onto a solid phase suitable for use in immunological assays, of a peptide antigen comprising two Cys residues "wherein thiol groups of the Cys residues are reversibly protected from oxidation by a chemically reversible means." Cosand teaches removal of benzyl-based protecting groups, by "conventional procedures," from a peptide bound to a t-butyloxy-carbonyl (BOCD)-methylbenzylcysteine-phenyl-acetamidomethyl (PA) polystyrene/divinlybenzene resin. As noted above, such conventional procedures entail removal of the protecting groups at the same time as cleavage of the peptide from the supporting resin by exposure of the resin-bound peptide to highly acidic conditions.

Further, Brugger teaches protection of SH-groups during peptide synthesis and removal of SH-group protection either during or at a final stage of synthesis. (*See, e.g.*, Brugger at column 8, lines 7-16.) Even these teachings in Brugger are primarily in the context of acid-labile protecting groups such as trityl (*see, e.g, id.*). Brugger briefly mentions ethylcarbmoyl protection, but again, only in a general context of protection of mecrapto groups of cysteine "in the manufacture" of the peptide (*see, e.g., id.* at column 3, lines 15-22, and column 4, lines 19-23.) There is no mention in Brugger of retaining protection of cysteine mercapto groups after peptide synthesis and after cleavage of the synthesized pepetide from a supporting resin.

For at least the reasons set forth above, Applicants believe claim 3 to be patentable under 35 U.S.C. § 103 over Cosand in view of Brugger. Withdrawal of the rejection is respectfully requested.

Cosand alone or in view of Neurath

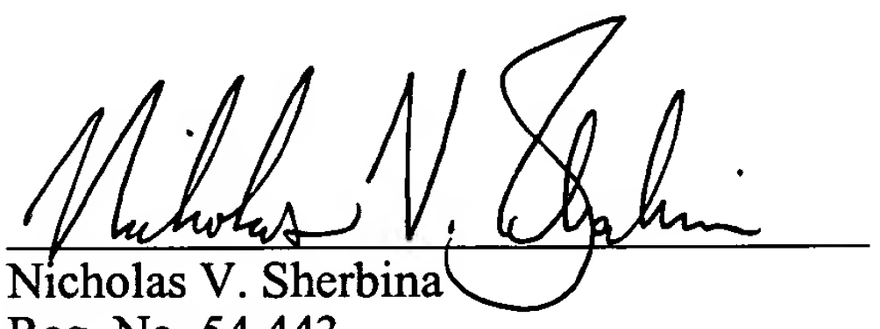
Claims 5 and 13 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cosand *et al.* in view of Neurath *et al.* (U.S. 4,861,588). In addition, claims 10, 11, and 13 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cosand *et al.*

Applicants believe the present rejections to be obviated in view of the amendments and remarks set forth above with respect to the rejection of claim 1 under 35 U.S.C. § 102. Because claim 1 (from which claims 5, 10, 11, and 13 indirectly depend) is believed to be patentable over Cosand for the reasons stated above, claims 5, 10, 11, and 13 are also believed to be patentable. In particular, Applicants note that a *prima facie* case of obviousness under 35 U.S.C. § 103 requires, *inter alia*, a teaching or suggestion of all claim limitations in the cited reference (or references when combined). (*See, e.g.*, MPEP § 2143.) In the present case, the primary reference, Cosand, does not teach or suggest all of the limitations of the base claim (claim 1) for at least the reasons set forth above. Accordingly, withdrawal of the rejections is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: September 21, 2005 By: 

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